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Original Article

Correlation of maintenance chemotherapy and improved survival in patients with locally advanced unresectable pancreatic head adenocarcinoma receiving neoadjuvant chemotherapy and concurrent chemoradiotherapy

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Abstract: To assess the efficacy of maintenance chemotherapy in the management of unresectable locally advanced pancreatic head adenocarcinoma (PHA) cancer after neoadjuvant chemotherapy and concurrent chemoradiation therapy (CCRT). This study, a large-scale head-to-head propensity score matching (PSM) cohort study, employed real-world data. PSM was used to evaluate the impact of maintenance chemotherapy on overall survival and cancer-specific survival in patients with unresectable locally advanced PHA who underwent neoadjuvant chemotherapy and CCRT. A total of 148 patients with locally advanced pancreatic head adenocarcinoma were included in the study after PSM. These patients were equally divided into two groups, those receiving maintenance chemotherapy and those who did not. Confounding factors were balanced between the groups. The adjusted hazard ratios for all-cause mortality and cancer-specific mortality were 0.56 (95% CI: 0.40-0.77; P = 0.0005) and 0.56 (95% CI: 0.40-0.78; P = 0.0007), respectively, in patients receiving maintenance chemotherapy compared to those who did not. Our large-scale, real-world study demonstrates that maintenance chemotherapy may enhance survival outcomes for patients with unresectable locally advanced pancreatic head adenocarcinoma who underwent neoadjuvant chemotherapy and concurrent chemoradiation therapy.

Keywords: Maintenance chemotherapy, pancreatic head adenocarcinoma, unresectable locally advanced, neoadjuvant chemotherapy, concurrent chemoradiation therapy

Introduction

In the United States, pancreatic cancer affects approximately 62,210 individuals each year, with a high proportion resulting in fatalities [1]. Pancreatic cancer ranks fourth among causes of cancer-related death in both men and women in the United States. Adenocarcinomas, originating from the ductal epithelium, are the most common type of pancreatic tumors, with 85% of these tumors being locoregionally advanced [1]. Potential resectability at diagnosis for pancreatic cancer occurs in only 15% to 20% of all cases, often limited by vascular invasion [1, 2]. For non-metastatic pancreatic cancer, surgical resection is the only available option. However, at the time of diagnosis, 40% of patients present with distant metastasis, while 30% to 40% present with locally advanced, non-resectable tumors [2]. The median survival duration for patients diagnosed with unresectable, locally advanced pancreatic cancer is limited to 8-12

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months, even when there is no presence of metastasis. This highlights the imperative requirement for the development of novel therapeutic approaches to enhance survival rates [3].

Presently, to the best of available information, there is no standard treatment option for patients suffering from unresectable locally advanced pancreatic cancer. The available treatments include neoadjuvant chemotherapy followed by surgical intervention after downstaging, chemotherapy as a standalone option, neoadjuvant chemotherapy combined with concurrent chemoradiotherapy, and maintenance chemotherapy [4-13]. Despite the presence of various treatment options, the survival rate for patients with unresectable locally advanced pancreatic cancer remains inadequate. From a radiation oncology viewpoint, a combination of neoadjuvant chemotherapy followed by concurrent chemoradiotherapy may prove more efficacious than systemic therapy solely. An increasing body of evidence supports the utilization of advanced radiotherapy techniques, such as intensity-modulated radiation therapy (IMRT) and image-guided radiotherapy (IGRT), to mitigate radiation-associated toxicities [9, 12-15]. Available information suggests the absence of a standard treatment for patients with unresectable locally advanced pancreatic cancer. The majority of studies examining the benefits of concurrent chemoradiotherapy (CCRT) for this condition have not employed a randomized controlled trial (RCT) design, owing to the challenges in accumulating a substantial patient population. The inclusion of concurrent chemoradiotherapy in the systemic treatment protocol for these patients may only result in a marginal improvement in survival, as stable or partial responses to treatment and residual tumors are commonly observed post-CCRT [9, 12-15]. Accordingly, in an effort to enhance patient survival, maintenance chemotherapy is being investigated as a therapeutic approach for eliminating residual tumors post-CCRT in patients suffering from unresectable locally advanced pancreatic cancer [16-23]. The metastasis rate in patients receiving neoadjuvant chemotherapy followed by CCRT remains high; maintenance chemotherapy may help eliminate microscopic metastatic pancreatic cancer cells. Thus, this therapy is often used after initial chemotherapy to prevent cancer recurrence [24]. Compared with the initial treatment regimen, maintenance chemotherapy is typically administered in small doses and over a long period; it is usually administered orally (pill) or intravenously [17-23, 25-27]. Maintenance chemotherapy may be beneficial for certain types of cancer, particularly those that are likely to recur [16, 19-21]. Notably, the benefits of maintenance chemotherapy may vary depending on the cancer type and patient population. In some cases, this therapy may not confer any additional benefit compared with the benefits of the initial treatment alone and may even cause side effects that reduce patients' quality of life [22, 23].

Presently, the available information does not indicate the existence of a standard treatment for patients with unresectable locally advanced pancreatic adenocarcinoma located within the head of the gland. To date, only a limited number of large-scale clinical trials have been conducted to assess the effectiveness of maintenance chemotherapy, administered post-concurrent chemoradiotherapy utilizing advanced radiotherapy techniques, in these patients. This is a crucial area of investigation given that over 60% of all pancreatic cancers occur in this location. However, previous studies on the application of maintenance chemotherapy for pancreatic cancer often encompass patients with metastatic disease, employ a diverse range of chemotherapy regimens, and consider various pancreatic locations, making it challenging to draw definitive conclusions regarding the impact of maintenance chemotherapy on the survival of patients with unresectable locally advanced pancreatic head adenocarcinoma (PHA) receiving neoadjuvant CCRT [3, 28-33]. In order to fill this deficiency in understanding, we performed a large-scale cohort study through head-to-head propensity score matching (PSM) analysis utilizing information obtained from a practical database. The study aimed to examine the impact of maintenance chemotherapy on the general survival and survival specific to cancer of individuals with unresectable locally advanced PHA, who received neoadjuvant chemotherapy followed by CCRT.

Patients and methods

Study cohort

The data used in this cohort study was sourced from the Taiwan Cancer Registry Database

(TCRD). The study included patients who were diagnosed with PHA between January 1, 2011 and December 31, 2018. The index date, used as a reference point, was established as the date of completion of CCRT for PHA. The follow-up period was from the index date to December 31, 2020. The TCRD, maintained by the Collaboration Center of Health Information Application under the Taiwanese Ministry of Health and Welfare, comprises comprehensive cancer-related information for patients, including clinical stage, treatment methodologies, chemotherapy regimens, chemotherapy dosages, cancer pathology, radiation modalities and doses, and treatment protocols [34-36]. The study protocols underwent review and received approval from the Institutional Review Board of the Tzu-Chi Medical Foundation (IRB109-015-B).

Selection and exclusion standards

The inclusion criteria for this study were: patients with a minimum age of 18 years, a diagnosis of PHA, and an unresectable clinical stage (as categorized in the eighth edition of the American Joint Committee on Cancer (AJCC) staging system, ranging from IB to III) without evidence of metastasis. PHA was defined as adenocarcinoma tissue located in the pancreatic head and confirmed through pathological examination. The determination of unresectability of PHA was pancreatic head tumor performed by professional general surgeons and was defined as locally advanced pancreatic cancer encasing more than 50% of the circumference of the superior mesenteric or celiac artery or causing occlusion of the superior mesenteric vein (SMV) or SMV-portal vein confluence, without the presence of suitable vessels for reconstruction above and below the tumor. The following were reasons for exclusion from the study: prior history of cancer prior to PHA diagnosis, missing data on sex, age less than 18 years, unclear staging information, missing information on smoking status and alcohol consumption, and non-adenocarcinoma histology. Moreover, we have included a clear explanation of the exclusion criteria and have also added Supplementary Figure 1, which displays a flowchart of the study.

Standard CCRT for PHA was established as gemcitabine-based chemotherapy in combination with radiation therapy, administered at a total dose of 50.4-61.2 Gy using the modern techniques of IMRT and IGRT [9]. All patients underwent neoadjuvant chemotherapy, adhering to the FOLFIRINOX regimen, which consisted of leucovorin calcium (folinic acid), fluorouracil, irinotecan hydrochloride, and oxaliplatin [5]. This was followed by CCRT. All the participants with a diagnosis of PHA in this study had an Eastern Cooperative Oncology Group Performance Status score of either 0 or 1. To eliminate potential bias in evaluating the impact of maintenance chemotherapy, patients who underwent pancreaticoduodenectomy after CCRT were excluded. The Charlson Comorbidity Index (CCI) was employed to assess the prevalence of comorbidities [37-39]. In our analysis, only comorbidities observed within six months prior to the index date were considered. The diagnoses recorded in the database were coded and classified based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) or ICD-10-CM, either at the time of initial admission or if a code was repeated more than twice during outpatient visits.

Maintenance chemotherapy

Maintenance chemotherapy was defined as the administration of the FOLFIRINOX regimen in patients with PHA after CCRT [3]. The lack of clear and definitive treatments for unresectable locally advanced PHA that receive neoadjuvant chemotherapy followed by CCRT makes the selection of maintenance chemotherapy challenging. Therefore, the choice of maintenance chemotherapy or regimens was made by the treating healthcare team based on various factors, including the patient's overall health status, cancer stage, and tolerance to chemotherapy. In this study, the number of sessions for maintenance chemotherapy was set at least 6 cycles over 6 months [3]. The maintenance chemotherapy group serves as the case group, while the no maintenance chemotherapy group, which underwent neoadjuvant chemotherapy followed by CCRT, is considered the control group.

PSM

To account for the influence of potential confounding factors, Propensity Score Matching (PSM) was conducted for the following con-

founders: age, sex, body mass index (BMI), year of diagnosis, AJCC clinical stage, smoking status, alcohol consumption, and Charlson Comorbidity Index (CCI) scores (as shown in **Table 1**). PSM was implemented using the greedy matching method at a 1:1 ratio with a caliper width of 0.2 [40]. Following PSM, patients were divided into two groups based on the receipt of maintenance chemotherapy: Group 1 comprised of patients who did not receive the therapy, while Group 2 comprised of those who did.

The outcome measures evaluated in the study

In this study, all-cause mortality and cancer-specific mortality served as the primary and secondary outcomes, respectively, among the patient population matched through the propensity score method.

Statistical examination

The Kaplan-Meier Method was employed to determine the cumulative incidence of all-cause and cancer-specific mortality in both Groups 1 and 2. Differences between the two groups were analyzed using the log-rank test. Univariate and multivariate Cox regression analyses were performed to calculate crude and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) for all-cause and cancer-specific mortality. The presentation of continuous variables is in the form of mean ± standard deviation, while categorical variables are reported as number and percentage. The data analysis was performed using SAS (version 9.4), and a two-tailed *P*-value less than 0.05 was considered statistically significant.

Results

Clinicopathological characteristics

In this study, 196 patients with locally advanced inoperable PHA who received neoadjuvant chemotherapy followed by CCRT were analyzed. The study population was divided into two groups, 115 patients in Group 1 and 81 patients in Group 2, based on receipt of maintenance chemotherapy. Propensity score matching (PSM) was performed to adjust for potential confounders, resulting in the inclusion of 74 patients in each group in the analysis. The baseline characteristics of the two groups before and after PSM are summarized in **Table 1**. Following PSM, the two groups demonstrated no significant differences in confounding factors, including age, sex, BMI, year of diagnosis, AJCC clinical stage, smoking status, alcohol consumption, and CCI scores. The median follow-up duration post index date was 2.02 years. The all-cause mortality rates were 98.6% in Group 1 and 89.2% in Group 2 (P < 0.0001). Cancer-specific mortality rates were 96.0% in Group 1 and 86.5% in Group 2 (P = 0.0421).

All-cause mortality

In this study, the effect of maintenance chemotherapy on all-cause mortality was analyzed in a cohort of 196 patients with unresectable locally advanced PHA who received neoadjuvant chemotherapy followed by CCRT. After propensity score matching (PSM), the study population comprised of 74 patients in each group (Group 1 and Group 2). Results showed that maintenance chemotherapy was a significant predictor of all-cause mortality. The adjusted hazard ratio (95% CI) for all-cause mortality was 0.56 (0.40-0.77; P = 0.0005) in Group 2 compared to Group 1.

Cancer-specific mortality

Maintenance chemotherapy was found to be a crucial independent predictor of cancer-specific mortality in our cohort. After PSM, the aHR (95% CI) for cancer-specific mortality in Group 2 was 0.56 (0.40-0.78; P = 0.0007) compared to Group 1.

Kaplan-Meier survival curves

The comparison of the two groups was carried out with regards to the survival rates, encompassing both overall survival and cancer-specific survival. Results showed that Group 2 had significantly higher 2-year overall survival rates (20.22%) in comparison to Group 1 (9.88%) with a significant *P*-value of < 0.0001 (refer to **Figure 1**). Additionally, the 2-year cancer-specific survival rates of Group 2 (27.33%) were also significantly higher than those of Group 1 (12.74%), with a significant *P*-value of < 0.0001 (refer to **Figure 2**). Thus, maintenance chemotherapy improved the survival outcomes in our cohort.

Discussion

Maintenance chemotherapy is often used after initial chemotherapy to prevent cancer recur-

Table 1. Characteristics of patients receiving maintenance chemotherapy and those not receiving it after neoadjuvant chemotherapy followed by concurrent chemoradiation therapy

Characteristics	Before Propensity Score Matching					After Propensity Score Matching				
	Patients Not Receiving Maintenance Chemotherapy (N = 115)		Patients Receiving Maintenance Chemotherapy (N = 81)		*P* value	Patients Not Receiving Maintenance Chemotherapy (N = 74)		Patients Receiving Maintenance Chemotherapy (N = 74)		*P* value
	n	%	n	%		n	%	n	%	
Age (years), mean ± SD	62.89 ± 10.94		62.94 ± 8.06		0.9714	62.13 ± 8.27		62.97 ± 8.27		0.9986
Age (years), median (IQR: Q1-Q3)	62.00 (56.00-71.00)		63.00 (59.00-69.00)		0.8072	62.15 (57.00-70.00)		62.50 (57.00-70.00)		0.9942
Age groups (years)					0.0908					0.6425
≤ 50	13	11.3	5	6.2		7	9.5	5	6.8	
51-60	39	33.9	23	28.4		21	28.4	22	29.7	
61-70	33	28.7	37	45.7		25	33.8	31	41.9	
≥ 70	30	26.1	16	19.8		21	28.4	16	21.6	
Sex					0.599					0.869
Female	51	44.4	39	48.2		34	46.0	33	44.6	
Male	64	55.7	42	51.9		40	54.1	41	55.4	
Body mass index (kg/m^2)					0.0221					0.5753
< 18.5	9	7.8	0	0.		0	0.0%	0	0.0%	
18.5-23	68	59.1	53	65.4		51	68.9%	50	67.6%	
24-26	22	19.1	23	28.		18	24.3%	19	25.7%	
≥ 27	16	13.9	5	6.2		5	6.8%	5	6.8%	
Years of diagnosis					0.4487					0.8582
2011-2013	40	34.8	24	29.6		23	31.1	22	29.7	
2014-2018	75	65.2	57	70.4		51	68.9	52	70.3	
American Joint Committee on Cancer clinical stage					0.8589					0.9999
IB	4	3.5	3	3.7		3	4.1	3	4.1	
IIA	13	11.3	8	9.9		7	9.5	7	9.5	
IIB	47	40.9	38	46.9		36	48.7	36	48.7	
III	51	44.4	32	39.5		28	37.8	28	37.8	
Smoking status					0.1493					0.8543
No	74	64.4	60	74.1		54	73.0	53	71.6	
Yes	41	35.7	21	25.9		20	27.0	21	28.4	
Alcohol consumption					0.3814					0.9999
No	90	78.3	59	72.8		55	74.3	55	74.3	
Yes	25	21.7	22	27.2		19	25.7	19	25.7	
CCI scores										
Mean (SD)	1.03 ± 1.23		0.99 ± 1.29		0.3237	1.03 ± 1.31		1.03 ± 1.30		0.8331
Median (IQR: Q1-Q3)	0.00 (0.00-2.00)		0.00 (0.00-2.00)		0.2783	0.00 (0.00-2.00)		0.00 (0.00-2.00)		0.7096

Number of patients with different CCI scores					0.5918					0.9999
0	58	50.4	44	54.3		39	52.7	39	52.7	
≥ 1	57	49.6	37	45.7		35	47.3	35	47.3	
Comorbidities										
Congestive heart failure	7	6.1	5	6.2	0.0995	5	6.8	5	6.8	0.9999
Dementia	0	0.0	0	0.0	0.9999	0	0.0	0	0.0	0.9999
Chronic pulmonary disease	19	16.5	10	12.4	0.4175	15	20.3	10	13.5	0.2727
Rheumatic disease	3	2.6	0	0.0	0.1430	3	4.1	0	0.0	0.0801
Liver disease	33	28.7	26	32.1	0.6090	25	33.8	24	32.4	0.8613
Diabetes with complications	10	8.7	5	6.2	0.5130	8	10.8	5	6.8	0.3836
Hemiplegia and paraplegia	0	0.0	0	0.0	0.9999	0	0.0	0	0.0	0.9999
Renal disease	8	7.0	3	3.7	0.3299	6	8.1	3	4.1	0.3021
Acquired immunodeficiency syndrome	0	0.0	0	0.0	0.9999	0	0.0	0	0.0	0.9999
Outcomes										
All-cause mortality					0.0702					< 0.0001
No	5	4.4	9	11.1		1	1.4	8	10.8	
Yes	110	95.7	72	88.9		73	98.6	66	89.2	
Cancer-specific mortality					0.0737					0.0421
No	7	6.1	11	13.6		3	4.1	10	13.5	
Yes	108	93.9	70	86.4		71	96.0	64	86.5	

Abbreviations: CCI, Charlson comorbidity index; SD, standard deviation; IQR, interquartile range.

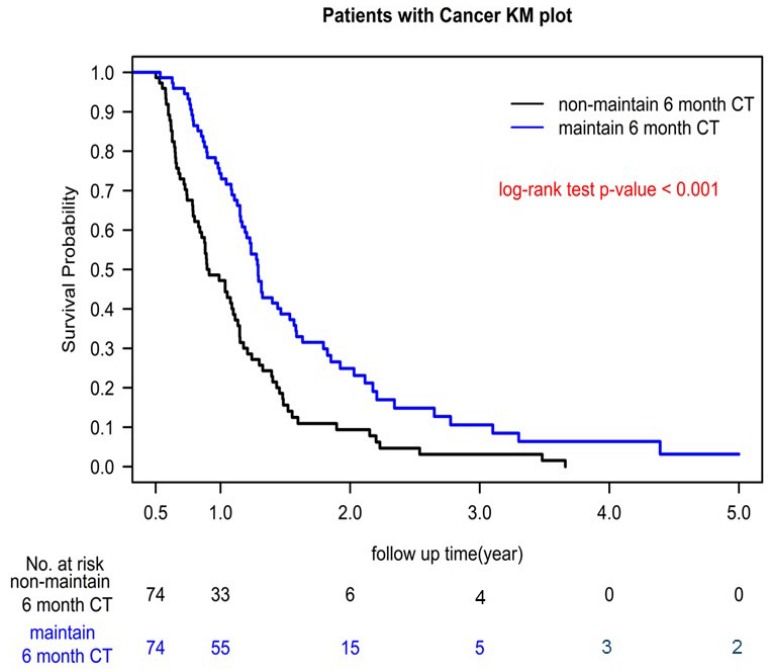

Figure 1. Kaplan-Meier overall survival curves for patients receiving maintenance chemotherapy and those not receiving it after neoadjuvant chemotherapy followed by concurrent chemoradiation therapy.

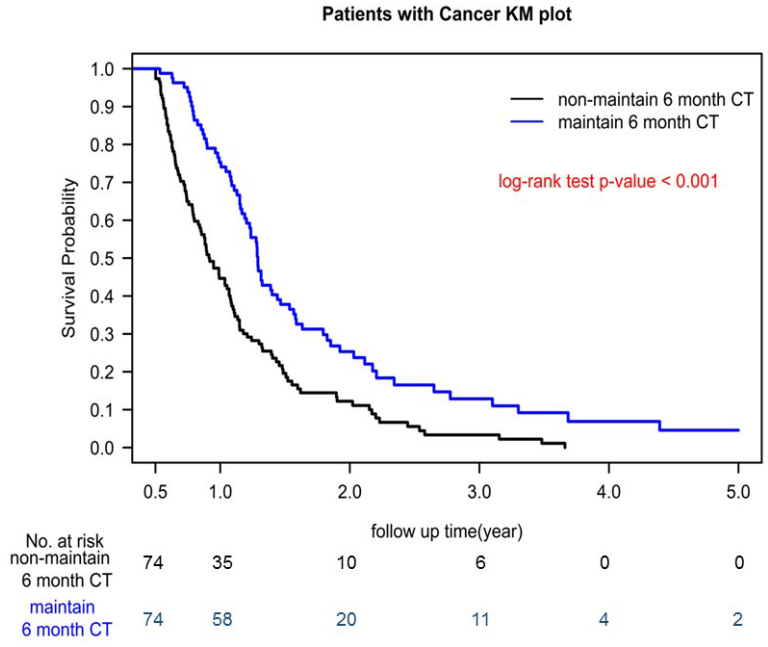

Figure 2. Kaplan-Meier cancer-specific survival curves for patients receiving maintenance chemotherapy and those not receiving it after neoadjuvant chemotherapy followed by concurrent chemoradiation therapy.

rence [16-23]. It involves the use of chemotherapy drugs to eradicate cancer cells that may not have been completely eliminated during the initial treatment. Maintenance chemotherapy has been demonstrated to be effective for some cancers [16, 19-21]. However, its use in pancreatic cancer, particularly for unresectable PHA without metastasis after CCRT, has not been widely studied. Standard treatment options for unresectable locally advanced PHA are inconsistent [4-13]. Resulting in poor survival rates. Further studies are necessary to improve survival outcomes in these patients. Neoadjuvant chemotherapy followed by CCRT may ensure higher rates of survival than systemic treatment alone [9, 12-15]. The majority of research on maintenance chemotherapy for pancreatic cancer has been centered on its impact on metastasis and various anatomical regions within the gland, including the head, body, and tail [3, 28-33]. In distinction, the focus of our study was exclusively on pancreatic adenocarcinoma located in the head of the pancreas. Our study, to the best of our knowledge, is the most extensive study utilizing Propensity Score Matching (PSM) to assess the survival outcomes of patients with unresectable PHA who received standard CCRT, and the administration of maintenance chemotherapy was comparatively more consistent in our study compared to other studies [3, 28-33]. Our findings suggest that maintenance chemotherapy administered according to the FOLFIRINOX regimen improves the survival rate of these patients (**Tables 2** and **3**).

The use of modern radiotherapy techniques in the administration of CCRT has been suggested to result in improved survival outcomes

Table 2. Cox proportional hazards regression model for all-cause mortality in propensity score-matched patients with unresectable locally advanced pancreatic head adenocarcinoma who received neoadjuvant chemotherapy followed by concurrent chemoradiation therapy

Characteristics	Crude HR (95% CI)	*P* value	Adjusted HR* (95% CI)	*P* value
Maintenance chemotherapy (reference, no)				
Yes	0.52 (0.39-0.71)	< 0.0001	0.56 (0.40-0.77)	0.0005
Age groups (reference, 18-50 years)				
51-60	0.92 (0.54-1.57)	0.7593	0.98 (0.54-1.75)	0.9350
61-70	0.69 (0.41-1.17)	0.1736	0.79 (0.44-1.41)	0.4230
> 70	1.04 (0.6-1.8)	0.9029	1.00 (0.56-1.78)	0.9861
Sex (reference, female)				
Male	0.98 (0.73-1.31)	0.8965	0.93 (0.63-1.36)	0.6914
Body mass index (reference, < 18.5 kg/m^2)				
18.5-23	1.21 (0.63-2.31)	0.5702	1.57 (0.78-3.15)	0.2049
24-26	1.08 (0.54-2.16)	0.8289	1.42 (0.68-2.96)	0.3445
≥ 27	1.66 (0.76-3.63)	0.2077	1.79 (0.79-4.04)	0.1641
Years of diagnosis (reference, 2011-2013)				
2014-2018	0.95 (0.7-1.29)	0.7344	0.97 (0.71-1.34)	0.8642
American Joint Committee on Cancer clinical stage (reference, stage IB)				
IIA	0.93 (0.39-2.2)	0.8661	0.89 (0.35-2.24)	0.8028
IIB	0.87 (0.4-1.89)	0.7253	0.91 (0.4-2.06)	0.8154
III	0.99 (0.46-2.15)	0.9823	0.97 (0.43-2.19)	0.9404
Smoking status (reference, no)				
Yes	1.11 (0.81-1.52)	0.5016	1.13 (0.74-1.72)	0.5779
Alcohol consumption (reference, no)				
Yes	1.02 (0.63-1.35)	0.6644	1.01 (0.47-1.78)	0.7898
CCI score (reference, CCI score = 0)				
≥ 1	1.14 (0.81-1.6)	0.4424	0.95 (0.64-1.42)	0.7999

Abbreviations: HR, hazard ratio; CI, confidence interval; aHR, adjusted hazard ratio; CCI, Charlson comorbidity index. *The model was adjusted for all covariates presented in **Table 2**.

for patients with locally advanced PHA compared to systemic treatment alone [9, 12-15]. Nevertheless, despite the implementation of CCRT, the survival rate of individuals with unresectable PHA remains unsatisfactory [9, 12-15]. Many patients who receive CCRT do not exhibit an apparent tumor response, although the overall survival may be increased [9, 12-15]. The enhancement in survival observed in some cases may be attributed to the slowing of the growth of pancreatic cancer cells subjected to radiation therapy. The residual pancreatic cancer cells present after CCRT may be targeted by maintenance chemotherapy. Thus, maintenance chemotherapy may improve both overall survival and cancer-specific survival. Limited observational studies, employing propensity score matching to mimic a RCT, have been performed on this subject. Moreover, most studies on maintenance chemotherapy for pancreatic cancer have focused on metastatic pancreatic cancer rather than locally advanced PHA [3, 28-33]. The benefits of maintenance chemotherapy on survival outcomes among patients with unresectable locally advanced PHA were observed to persist after PSM analysis. This suggests that the therapy may be advantageous, particularly for individuals with non-metastatic PHA. To establish the validity of these findings, well-designed RCTs should be conducted in the future. The results of the current study may serve as a benchmark for future RCTs.

The primary strength of our study lies in its specificity in focusing on unresectable locally advanced pancreatic adenocarcinoma located in the head of the pancreas, as opposed to cancers situated at various sites in the pancreas, multiple types of pancreatic cancer, and metastatic pancreatic cancer. This specificity has enabled us to produce accurate and pertinent results. This is the first study utilizing PSM to examine the impact of maintenance chemotherapy on the survival of patients with unresectable PHA who received neoadjuvant chemotherapy and CCRT. Our findings underscore the significance of exploring novel therapies to

Table 3. Cox proportional hazards regression model for cancer-specific mortality in propensity score-matched patients with unresectable locally advanced pancreatic head adenocarcinoma who received neoadjuvant chemotherapy followed by concurrent chemoradiation therapy

Characteristics	Crude HR (95% CI)	*P* value	Adjusted HR* (95% CI)	*P* value
Maintenance chemotherapy (reference, no)				
Yes	0.52 (0.38-0.71)	< 0.0001	0.56 (0.40-0.78)	0.0007
Age groups (reference, 18-50 years)				
51-60	0.92 (0.54-1.57)	0.7618	0.97 (0.54-1.74)	0.9087
61-70	0.66 (0.39-1.12)	0.1241	0.74 (0.41-1.33)	0.3177
> 70	1.01 (0.58-1.76)	0.9670	0.96 (0.54-1.73)	0.8987
Sex (reference, female)				
Male	0.96 (0.72-1.29)	0.8059	0.90 (0.61-1.33)	0.5889
Body mass index (reference, < 18.5 kg/m^2)				
18.5-23	1.17 (0.61-2.23)	0.6418	1.56 (0.77-3.15)	0.2125
24-26	1.08 (0.54-2.16)	0.8291	1.46 (0.7-3.05)	0.3137
≥ 27	1.66 (0.76-3.64)	0.2069	1.80 (0.79-4.09)	0.1589
Years of diagnosis (reference, 2011-2013)				
2014-2018	0.94 (0.69-1.28)	0.6991	0.97 (0.7-1.34)	0.8466
American Joint Committee on Cancer clinical stage (reference, stage IB)				
IIA	0.93 (0.39-2.21)	0.8743	0.88 (0.35-2.21)	0.7800
IIB	0.84 (0.39-1.83)	0.6609	0.86 (0.38-1.97)	0.7242
III	0.98 (0.45-2.13)	0.9616	0.94 (0.42-2.13)	0.8849
Smoking status (reference, no)				
Yes	1.12 (0.82-1.54)	0.4751	1.12 (0.73-1.72)	0.5908
Alcohol consumption (reference, no)				
Yes	0.88 (0.62-1.25)	0.4795	0.84 (0.52-1.36)	0.4850
CCI score (reference, CCI score = 0)				
≥ 1	1.16 (0.86-1.55)	0.3392	1.05 (0.76-1.45)	0.7672

Abbreviations: HR, hazard ratio; CI, confidence interval; aHR, adjusted hazard ratio; CCI, Charlson comorbidity index. *The model was adjusted for all covariates presented in **Table 2**.

enhance the survival rate of patients with unresectable PHA who received neoadjuvant chemotherapy and CCRT.

The present study is subject to certain limitations. First, an evaluation of the toxicity of the treatments was not performed, which may have impacted treatment-related mortality and potentially influenced the estimates. If the addition of maintenance chemotherapy is accompanied by increased treatment-related toxicity, the overall survival will decrease. In this case, the effects of maintenance chemotherapy on patient survival might be underestimated, but our conclusions would not be overturned. Second, the study population consisted solely of Asian patients; thus, the generalizability of our findings to other ethnic groups remains unclear. Third, the patients' comorbidities were diagnosed as per ICD9-CM or ICD-10-CM codes, whose accuracy could not be confirmed. However, the TCRD verifies the accuracy of diagnoses through chart reviews and patient interviews; hospitals with discrepant records and those engaging in malpractice may face penalties. Finally, although the possibility of selection bias, which includes potential biases in patient selection or unmeasured confounding variables, cannot be ignored in this study, the effects of confounding variables were accounted for using PSM. Patients with similar levels of physical activity, as indicated by their Performance Status, were carefully selected to minimize the impact of confounding factors. Nonetheless, to determine the efficacy of maintenance chemotherapy in this patient population with certainty, large-scale randomized controlled trials that involve appropriate patient selection and treatment protocols are necessary.

Conclusions

Maintenance chemotherapy utilizing the FOLFIRINOX regimen appears to enhance the survival rate of patients with unresectable locally advanced PHA who received neoadjuvant chemotherapy followed by CCRT. However, further investigations are necessary to comprehend the full potential benefits and drawbacks of this therapeutic option for this patient population. In the future, large-scale RCTs should be conducted to confirm and extend our findings.

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Disclosure of conflict of interest

None.

Abbreviations

CCRT, concurrent chemoradiotherapy; BMI, body mass index; AJCC, American Joint Committee on Cancer; PSM, propensity score matching; CI, confidence interval; aHR, adjusted hazard ratio; TCRD, Taiwan Cancer Registry Database; CCI, Charlson comorbidity index; ICD-9-CM, *International Classification of Diseases, Ninth Revision, Clinical Modification*; ICD-10-CM, *International Classification of Diseases, Tenth Revision, Clinical Modification*; HR, hazard ratio; PHA, pancreatic head adenocarcinoma.

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References

[1] Siegel RL, Miller KD, Fuchs HE and Jemal A. Cancer statistics, 2022. CA Cancer J Clin 2022; 72: 7-33.

[2] Blackford AL, Canto MI, Klein AP, Hruban RH and Goggins M. Recent trends in the incidence and survival of stage 1A pancreatic cancer: a surveillance, epidemiology, and end results analysis. J Natl Cancer Inst 2020; 112: 1162-1169.

[3] Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardiere C, Bennouna J, Bachet JB, Khemissa-Akouz F, Pere-Verge D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C and Ducreux M; Groupe Tumeurs Digestives of Unicancer; PRODIGE Intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011; 364: 1817-1825.

[4] Conroy T, Paillot B, Francois E, Bugat R, Jacob JH, Stein U, Nasca S, Metges JP, Rixe O, Michel P, Magherini E, Hua A and Deplanque G. Irinotecan plus oxaliplatin and leucovorin-modulated fluorouracil in advanced pancreatic cancer-a Groupe Tumeurs Digestives of the Federation Nationale des Centres de Lutte Contre le Cancer study. J Clin Oncol 2005; 23: 1228-1236.

[5] Marthey L, Sa-Cunha A, Blanc JF, Gauthier M, Cueff A, Francois E, Trouilloud I, Malka D, Bachet JB, Coriat R, Terrebonne E, De La Fouchardiere C, Manfredi S, Solub D, Lecaille C, Thirot Bidault A, Carbonnel F and Taieb J. FOLFIRINOX for locally advanced pancreatic adenocarcinoma: results of an AGEO multicenter prospective observational cohort. Ann Surg Oncol 2015; 22: 295-301.

[6] Ferrone CR, Marchegiani G, Hong TS, Ryan DP, Deshpande V, McDonnell EI, Sabbatino F, Santos DD, Allen JN, Blaszkowsky LS, Clark JW, Faris JE, Goyal L, Kwak EL, Murphy JE, Ting DT, Wo JY, Zhu AX, Warshaw AL, Lillemoe KD and Fernandez-del Castillo C. Radiological and surgical implications of neoadjuvant treatment with FOLFIRINOX for locally advanced and borderline resectable pancreatic cancer. Ann Surg 2015; 261: 12-17.

[7] Suker M, Beumer BR, Sadot E, Marthey L, Faris JE, Mellon EA, El-Rayes BF, Wang-Gillam A, Lacy J, Hosein PJ, Moorcraft SY, Conroy T, Hohla F, Allen P, Taieb J, Hong TS, Shridhar R, Chau I, van Eijck CH and Koerkamp BG. FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and patient-level meta-analysis. Lancet Oncol 2016; 17: 801-810.

[8] Janssen QP, van Dam JL, Doppenberg D, Prakash LR, van Eijck CHJ, Jarnagin WR, O'Reilly EM, Paniccia A, Besselink MG, Katz MHG, Tzeng CD, Wei AC, Zureikat AH and Groot Koerkamp B; Trans-Atlantic Pancreatic Surgery (TAPS) Consortium. FOLFIRINOX as initial treatment for localized pancreatic adenocarcino-

ma: a retrospective analysis by the trans-atlantic pancreatic surgery consortium. J Natl Cancer Inst 2022; 114: 695-703.
[9] Li CP, Chao Y, Chi KH, Chan WK, Teng HC, Lee RC, Chang FY, Lee SD and Yen SH. Concurrent chemoradiotherapy treatment of locally advanced pancreatic cancer: gemcitabine versus 5-fluorouracil, a randomized controlled study. Int J Radiat Oncol Biol Phys 2003; 57: 98-104.
[10] Motoi F, Ishida K, Fujishima F, Ottomo S, Oikawa M, Okada T, Shimamura H, Takemura S, Ono F, Akada M, Nakagawa K, Katayose Y, Egawa S and Unno M. Neoadjuvant chemotherapy with gemcitabine and S-1 for resectable and borderline pancreatic ductal adenocarcinoma: results from a prospective multiinstitutional phase 2 trial. Ann Surg Oncol 2013; 20: 3794-3801.
[11] Seufferlein T, Bachet JB, Van Cutsem E and Rougier P; ESMO Guidelines Working Group. Pancreatic adenocarcinoma: ESMO-ESDO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012; 23 Suppl 7: vii33-40.
[12] Mukherjee S, Hurt CN, Bridgewater J, Falk S, Cummins S, Wasan H, Crosby T, Jephcott C, Roy R, Radhakrishna G, McDonald A, Ray R, Joseph G, Staffurth J, Abrams RA, Griffiths G and Maughan T. Gemcitabine-based or capecitabine-based chemoradiotherapy for locally advanced pancreatic cancer (SCALOP): a multicentre, randomised, phase 2 trial. Lancet Oncol 2013; 14: 317-326.
[13] Ikeda M, Ioka T, Ito Y, Yonemoto N, Nagase M, Yamao K, Miyakawa H, Ishii H, Furuse J, Sato K, Sato T and Okusaka T. A multicenter phase II trial of S-1 with concurrent radiation therapy for locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys 2013; 85: 163-169.
[14] Lin YK, Hsieh MC, Chang CL, Chow JM, Yuan KS, Wu ATH and Wu SY. Intensity-modulated radiotherapy with systemic chemotherapy improves survival in patients with nonmetastatic unresectable pancreatic adenocarcinoma: a propensity score-matched, nationwide, population-based cohort study. Radiother Oncol 2018; 129: 326-332.
[15] Hsieh MC, Chang WW, Yu HH, Lu CY, Chang CL, Chow JM, Chen SU, Cheng Y and Wu SY. Adjuvant radiotherapy and chemotherapy improve survival in patients with pancreatic adenocarcinoma receiving surgery: adjuvant chemotherapy alone is insufficient in the era of intensity modulation radiation therapy. Cancer Med 2018; 7: 2328-2338.
[16] Perol M, Chouaid C, Perol D, Barlesi F, Gervais R, Westeel V, Crequit J, Lena H, Vergnenegre A, Zalcman G, Monnet I, Le Caer H, Fournel P, Falchero L, Poudenx M, Vaylet F, Segura-Ferlay C, Devouassoux-Shisheboran M, Taron M and Milleron B. Randomized, phase III study of gemcitabine or erlotinib maintenance therapy versus observation, with predefined second-line treatment, after cisplatin-gemcitabine induction chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol 2012; 30: 3516-3524.
[17] Goldstone AH, Richards SM, Lazarus HM, Tallman MS, Buck G, Fielding AK, Burnett AK, Chopra R, Wiernik PH, Foroni L, Paietta E, Litzow MR, Marks DI, Durrant J, McMillan A, Franklin IM, Luger S, Ciobanu N and Rowe JM. In adults with standard-risk acute lymphoblastic leukemia, the greatest benefit is achieved from a matched sibling allogeneic transplantation in first complete remission, and an autologous transplantation is less effective than conventional consolidation/maintenance chemotherapy in all patients: final results of the International ALL Trial (MRC UKALL XII/ECOG E2993). Blood 2008; 111: 1827-1833.
[18] Shin HJ, Chung JS and Cho GJ. Imatinib interim therapy between chemotherapeutic cycles and in vivo purging prior to autologous stem cell transplantation, followed by maintenance therapy is a feasible treatment strategy in Philadelphia chromosome-positive acute lymphoblastic leukemia. Bone Marrow Transplant 2005; 36: 917-918.
[19] Zinner RG, Obasaju CK, Spigel DR, Weaver RW, Beck JT, Waterhouse DM, Modiano MR, Hrinczenko B, Nikolinakos PG, Liu J, Koustenis AG, Winfree KB, Melemed SA, Guba SC, Ortuzar WI, Desaiah D, Treat JA, Govindan R and Ross HJ. PRONOUNCE: randomized, open-label, phase III study of first-line pemetrexed + carboplatin followed by maintenance pemetrexed versus paclitaxel + carboplatin + bevacizumab followed by maintenance bevacizumab in patients ith advanced nonsquamous non-small-cell lung cancer. J Thorac Oncol 2015; 10: 134-142.
[20] Ciuleanu T, Brodowicz T, Zielinski C, Kim JH, Krzakowski M, Laack E, Wu YL, Bover I, Begbie S, Tzekova V, Cucevic B, Pereira JR, Yang SH, Madhavan J, Sugarman KP, Peterson P, John WJ, Krejcy K and Belani CP. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. Lancet 2009; 374: 1432-1440.
[21] Paz-Ares L, de Marinis F, Dediu M, Thomas M, Pujol JL, Bidoli P, Molinier O, Sahoo TP, Laack E, Reck M, Corral J, Melemed S, John W, Chouaki N, Zimmermann AH, Visseren-Grul C

and Gridelli C. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. Lancet Oncol 2012; 13: 247-255.

[22] Seto T, Azuma K, Yamanaka T, Sugawara S, Yoshioka H, Wakuda K, Atagi S, Iwamoto Y, Hayashi H, Okamoto I, Saka H, Mitsuoka S, Fujimoto D, Nishino K, Horiike A, Daga H, Sone T, Yamamoto N, Nakagawa K and Nakanishi Y. Randomized phase III study of continuation maintenance bevacizumab with or without pemetrexed in advanced nonsquamous non-small-cell lung cancer: COMPASS (WJOG5610L). J Clin Oncol 2020; 38: 793-803.

[23] Cicenas S, Geater SL, Petrov P, Hotko Y, Hooper G, Xia F, Mudie N and Wu YL. Maintenance erlotinib versus erlotinib at disease progression in patients with advanced non-small-cell lung cancer who have not progressed following platinum-based chemotherapy (IUNO study). Lung Cancer 2016; 102: 30-37.

[24] Mei L, Chen H, Wei DM, Fang F, Liu GJ, Xie HY, Wang X, Zou J, Han X and Feng D. Maintenance chemotherapy for ovarian cancer. Cochrane Database Syst Rev 2013; 2013: CD007414.

[25] Lu B, Bao LB, Sun Z, Hua ZL, Wang X and Qu CP. Efficacy and safety of capecitabine as maintenance therapy after capecitabine-based combination chemotherapy for patients with advanced esophagogastric junction adenocarcinoma. Eur Rev Med Pharmacol Sci 2015; 19: 3605-3612.

[26] Petrioli R, Francini E, Roviello F, Marrelli D, Miano ST, Fiaschi AI, Laera L, Bellini MA and Roviello G. Treatment of advanced oesophagogastric cancer with FOLFOX-4 regimen followed by leucovorin/bolus and continuous infusion 5-FU as maintenance chemotherapy in patients aged ≥ 75 years with impaired performance status. J Geriatr Oncol 2015; 6: 380-386.

[27] Chi D, Chen B, Guo S, Bai K, Ma H, Hu Y, Li Q and Zhu Y. Oral maintenance therapy using apatinib combined with S-1/capecitabine for esophageal squamous cell carcinoma with residual disease after definitive chemoradiotherapy. Aging (Albany NY) 2021; 13: 8408-8420.

[28] Golan T, Hammel P, Reni M, Van Cutsem E, Macarulla T, Hall MJ, Park JO, Hochhauser D, Arnold D, Oh DY, Reinacher-Schick A, Tortora G, Algul H, O'Reilly EM, McGuinness D, Cui KY, Schlienger K, Locker GY and Kindler HL. Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. N Engl J Med 2019; 381: 317-327.

[29] Hammel P, Vitellius C, Boisteau E, Wisniewski M, Colle E, Hilmi M, Dengremont C, Granier S, Turpin A, de Mestier L and Neuzillet C. Maintenance therapies in metastatic pancreatic cancer: present and future with a focus on PARP inhibitors. Ther Adv Med Oncol 2020; 12: 1758835920937949.

[30] Shi Y, Han Q, Yan H, Lv Y, Yuan J, Li J, Guan S, Wang Z, Huang L and Dai G. S-1 maintenance therapy after first-line treatment with nab-paclitaxel plus S-1 for advanced pancreatic adenocarcinoma: a real-world study. Front Oncol 2022; 12: 865404.

[31] Dahan L, Williet N, Le Malicot K, Phelip JM, Desrame J, Bouche O, Petorin C, Malka D, Rebischung C, Aparicio T, Lecaille C, Rinaldi Y, Turpin A, Bignon AL, Bachet JB, Seitz JF, Lepage C and Francois E; PRODIGE 35 Investigators/Collaborators. Randomized phase II trial evaluating two sequential treatments in first line of metastatic pancreatic cancer: results of the PANOPTIMOX-PRODIGE 35 trial. J Clin Oncol 2021; 39: 3242-3250.

[32] Vaccaro V, Sperduti I and Milella M. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011; 365: 768-769.

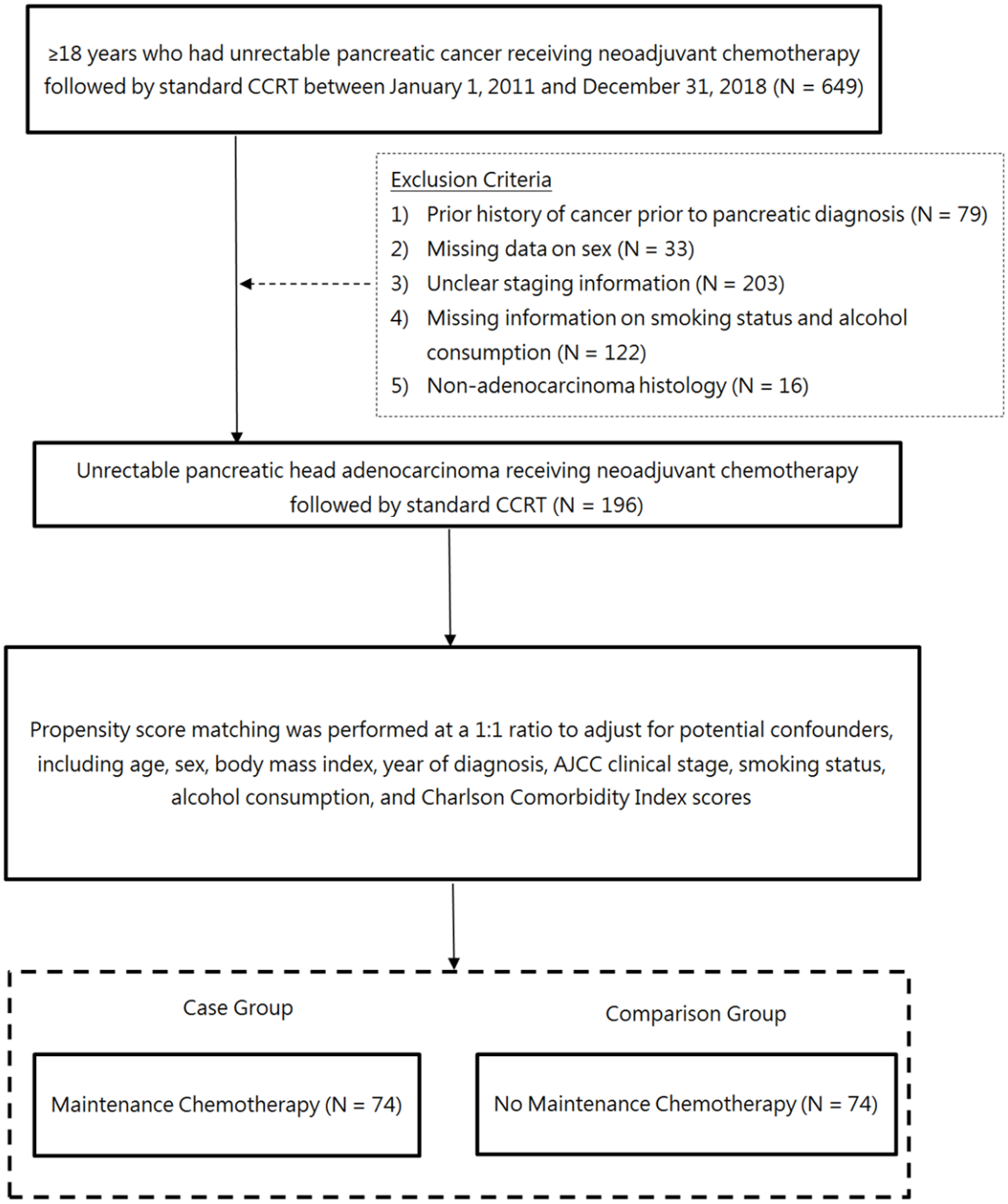
[33] Reiss KA, Mick R, O'Hara MH, Teitelbaum U, Karasic TB, Schneider C, Cowden S, Southwell T, Romeo J, Izgur N, Hannan ZM, Tondon R, Nathanson K, Vonderheide RH, Wattenberg MM, Beatty G and Domchek SM. Phase II study of maintenance rucaparib in patients with platinum-sensitive advanced pancreatic cancer and a pathogenic germline or somatic variant in BRCA1, BRCA2, or PALB2. J Clin Oncol 2021; 39: 2497-2505.

[34] Lin WC, Ding YF, Hsu HL, Chang JH, Yuan KS, Wu ATH, Chow JM, Chang CL, Chen SU and Wu SY. Value and application of trimodality therapy or definitive concurrent chemoradiotherapy in thoracic esophageal squamous cell carcinoma. Cancer 2017; 123: 3904-3915.

[35] Yen YC, Chang JH, Lin WC, Chiou JF, Chang YC, Chang CL, Hsu HL, Chow JM, Yuan KS, Wu ATH and Wu SY. Effectiveness of esophagectomy in patients with thoracic esophageal squamous cell carcinoma receiving definitive radiotherapy or concurrent chemoradiotherapy through intensity-modulated radiation therapy techniques. Cancer 2017; 123: 2043-2053.

[36] Chang CL, Tsai HC, Lin WC, Chang JH, Hsu HL, Chow JM, Yuan KS, Wu ATH and Wu SY. Dose escalation intensity-modulated radiotherapy-based concurrent chemoradiotherapy is effec-

tive for advanced-stage thoracic esophageal squamous cell carcinoma. Radiother Oncol 2017; 125: 73-79.
[37] Zhang J, Lu CY, Chen HM and Wu SY. Neoadjuvant chemotherapy or endocrine therapy for invasive ductal carcinoma of the breast with high hormone receptor positivity and human epidermal growth factor receptor 2 negativity. JAMA Netw Open 2021; 4: e211785.
[38] Chen WM, Chen M, Hsu JG, Lee TS, Shia BC and Wu SY. Use of preoperative FDG PET/CT and survival of patients with resectable non-small cell lung cancer. Radiology 2022; 305: 219-227.
[39] Liu WC, Liu HE, Kao YW, Qin L, Lin KC, Fang CY, Tsai LL, Shia BC and Wu SY. Definitive radiotherapy or surgery for early oral squamous cell carcinoma in old and very old patients: a propensity-score-matched, nationwide, population-based cohort study. Radiother Oncol 2020; 151: 214-221.
[40] Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharm Stat 2011; 10: 150-161.



Supplementary Figure 1. Study flow-chart.